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FILE 'HOME' ENTERED AT 03:27:24 ON 01 AUG 2003

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FILE 'CAPLUS' ENTERED AT 03:27:45 ON 01 AUG 2003
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=> opioid receptor heterodimeriz?
L1            1 OPIOID RECEPTOR HETERODIMERIZ?

=> d l1 ti abs so

L1   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS on STN
TI   Heterodimerization of somatostatin and opioid receptors cross-modulates
     phosphorylation, internalization, and desensitization
AB   Heterodimerization has been shown to modulate the ligand binding,
     signaling, and trafficking properties of G protein-coupled receptors.
     However, to what extent heterodimerization may alter agonist-induced
     phosphorylation and desensitization of these receptors has not been
     documented.  We have recently shown that heterodimerization of sst2A and
     sst3 somatostatin receptors results in inactivation of sst3 receptor
     function.  Here we examine dimerization of the sst2A somatostatin receptor
     and the .mu.-opioid receptor, members of closely related G protein-coupled
     receptor families.  In coimmunopptn. studies using differentially
     epitope-tagged receptors, we provide direct evidence for
     heterodimerization of sst2A and MOR1 in human embryonic kidney 293 cells.
     Unlike heteromeric assembly of sst2A and sst3, sst2A-MOR1
     heterodimerization did not substantially alter the ligand binding or
     coupling properties of these receptors.  However, exposure of the
     sst2A-MOR1 heterodimer to the sst2A-selective ligand L-779976 induced
     phosphorylation, internalization, and desensitization of sst2A as well as
     MOR1.  Similarly, exposure of the sst2A-MOR1 heterodimer to the
     .mu.-selective ligand [D-Ala2,Me-Phe4,Gly5-ol]enkephalin induced
     phosphorylation and desensitization of both MOR1 and sst2A but not
     internalization of sst2A.  Cross-phosphorylation and cross-desensitization
     of the sst2A-MOR1 heterodimer were selective; they were neither obsd. with
     the sst2A-sst3 heterodimer nor with the endogenously expressed
     lysophosphatidic acid receptor.  Heterodimerization may thus represent a
     novel regulatory mechanism that could either restrict or enhance
     phosphorylation and desensitization of G protein-coupled receptors.
SO   Journal of Biological Chemistry (2002), 277(22), 19762-19772
     CODEN: JBCHA3; ISSN: 0021-9258


=> opioid receptor
L2        39077 OPIOID RECEPTOR

=> heterodimeriz?
L3         5042 HETERODIMERIZ?

=> l2 and l3
L4           22 L2 AND L3
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=> l4 and 1970-1999/py
   2 FILES SEARCHED...
L5   3 L4 AND 1970-1999/PY

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6   1 DUP REM L5 (2 DUPLICATES REMOVED)

=> d ti abs so l6

L6   ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
     DUPLICATE 1
TI   G-protein-coupled receptor **heterodimerization** modulates receptor
     function.
AB   The opioid system modulates several physiological processes, including
     analgesia, the stress response, the immune response and neuroendocrine
     function. Pharmacological and molecular cloning studies have identified
     three **opioid-receptor** types, delta, kappa and mu, that
     mediate these diverse effects. Little is known about the ability of the
     receptors to interact to form new functional structures, the simplest of
     which would be a dimer. Structural and biochemical studies show that other
     G-protein-coupled receptors (GPCRs) interact to form homodimers. Moreover,
     two non-functional receptors **heterodimerize** to form a functional
     receptor, suggesting that dimerization is crucial for receptor function.
     However, **heterodimerization** between two fully functional
     receptors has not been documented. Here we provide biochemical and
     pharmacological evidence for the **heterodimerization** of two fully
     functional **opioid receptors**, kappa and delta. This
     results in a new receptor that exhibits ligand binding and
     functionalproperties that are distinct from those of either receptor.
     Furthermore, the kappa-delta heterodimer synergistically binds highly
     selective agonists and potentiates signal transduction. Thus,
     heterodimerization of these GPCRs represents a novel mechanism
     that modulates their function.
SO   Nature (London), (**June 17, 1999**) Vol. 399, No. 6737, pp.
     697-700.
     ISSN: 0028-0836.

=> opioid adrenergic dimeriz?
L7   0 OPIOID ADRENERGIC DIMERIZ?

=> adrenergic heterodimeriz?
L8   0 ADRENERGIC HETERODIMERIZ?

=> adrenergic receptor
L9   68939 ADRENERGIC RECEPTOR

=> l3 and l9
L10   23 L3 AND L9

=> l10 and 1970-1999/py
   2 FILES SEARCHED...
L11   3 L10 AND 1970-1999/PY

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12   1 DUP REM L11 (2 DUPLICATES REMOVED)

=> d ti abs so l12

L12 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
     DUPLICATE 1
TI   Functional rescue of a constitutively desensitized beta2AR through
     receptor dimerization.

AB We have recently demonstrated that wild-type beta2-**adrenergic receptors** (beta2AR) form homodimers and that disruption of receptor dimerization inhibits signalling via Gs (Hebert, Moffett, Morello, Loisel, Bichet, Barret and Bouvier (1996) J. Biol. Chem. 271, 16384-16392). Here taking advantage of the altered functional properties of a non-palmitoylated, constitutively desensitized mutant beta2AR (C341Gbeta2AR), we sought to study whether physical interactions between mutant and wild-type beta2AR expressed in Sf9 cells could occur and have functional consequences. Using metabolic labelling with (3H)palmitate and co-immunoprecipitation we demonstrated the existence of **heterodimerization** between wild-type and C341Gbeta2AR. Furthermore, we show that, in co-expression experiments, wild-type receptors have a dominant positive effect resulting in the functional complementation of C341Gbeta2AR. Indeed, when expressed alone, the mutant C341G receptor displays altered functional characteristics in that (1) the response of the receptor to agonist is reduced as compared to the wild-type receptor and (2) the desensitization of the receptor in response to prolonged exposure to agonist is minimal. In contrast, when C341G and the wild-type beta2AR were expressed together, both the response to agonist and subsequent desensitization (at a constant level of total receptor) were equivalent to the wild-type beta2AR expressed alone. This dominant positive effect was also seen when C341G was co-expressed with a second receptor mutant in which the two protein kinase A phosphorylation sites (S261, 262, 345, 346A beta2AR) were mutated. Taken together these data suggest that intermolecular interactions between receptors may have both functional and structural implications for G-protein-mediated signalling.

SO Biochemical Journal, (**Feb. 15, 1998**) Vol. 330, No. 1, pp. 287-293.
ISSN: 0264-6021.

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=> devi?/au and lakshmi?/au
L13          46 DEVI?/AU AND LAKSHMI?/AU

=> l3 and l13
L14           0 L3 AND L13

=> bryen?/au and jordan?/au
L15           0 BRYEN?/AU AND JORDAN?/AU

=> d his

     (FILE 'HOME' ENTERED AT 03:27:24 ON 01 AUG 2003)

     FILE 'BIOSIS, MEDLINE, CAPLUS' ENTERED AT 03:27:45 ON 01 AUG 2003
L1             1 OPIOID RECEPTOR HETERODIMERIZ?
L2         39077 OPIOID RECEPTOR
L3          5042 HETERODIMERIZ?
L4            22 L2 AND L3
L5             3 L4 AND 1970-1999/PY
L6             1 DUP REM L5 (2 DUPLICATES REMOVED)
L7             0 OPIOID ADRENERGIC DIMERIZ?
L8             0 ADRENERGIC HETERODIMERIZ?
L9         68939 ADRENERGIC RECEPTOR
L10           23 L3 AND L9
L11            3 L10 AND 1970-1999/PY
L12            1 DUP REM L11 (2 DUPLICATES REMOVED)
L13           46 DEVI?/AU AND LAKSHMI?/AU
L14            0 L3 AND L13
L15            0 BRYEN?/AU AND JORDAN?/AU

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WEST Search History

DATE: Friday, August 01, 2003

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L6	bryen.in. and jordan.in.	0	L6
L5	devi.in. and lakshmi.in.	2	L5
L4	opioid and heterodimerization	5	L4
L3	l1 and L2	0	L3
L2	heterodimerize or heterodimerization	603	L2
L1	opioid adj receptor	817	L1

END OF SEARCH HISTORY